REMARKS

The Status of the Claims.

Claims 6-8, and 87-101 are pending with entry of this amendment, claims 1, 3, 4, and 19 being canceled herein and claims 94-101 being added herein. Claims 6-8, and 87-91 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 6, 7, and 8, support for a pharmaceutically acceptable carrier can be found throughout the specification. For example, see specification at page 42, line 3 to page 44, line 2, and originally filed claim 19. With respect to claims 6 and 7, support for "wherein the N-terminal amino acid sequence comprises a subsequence of residues of 1-36 of SEQ ID NO.: 5 or residues 1-38 of SEQ ID NO.: 4" can be found throughout the specification, e.g., at page 11, lines 28-30, and at page 25, line 21 to page 26, line 25. Claims 88 and 90 are amended to include the language "consists of." Support can be found throughout the specification, e.g., at page 27, lines 12-21. Other amendments to claims 6, 7, 89, and 91 are made to incorporate the elements of the corresponding independent claim, e.g., claim 1. With respect to claims 8, 88, and 90, these claims are amended to incorporate the elements of the corresponding independent claim or other dependent claims, except for those elements that are inherent in the sequences recited in these claims, which have been omitted in the interest of greater clarity. Claim 87 was amended to change the dependency to claims currently pending with the entry of this amendment. With respect to claims 94 and 97, support for "wherein the N-terminal amino acid sequence comprises the subsequence of residues 1-36 of SEQ ID NO.: 5" can be found throughout the specification, e.g., at page 11, lines 28-30, and at page 25, line 21 to page 26, line 25. With respect to claims 95 and 98, support for "wherein the N-terminal amino acid sequence comprises the subsequence of residues 1-38 of SEQ ID NO.: 4" can be found throughout the specification, e.g., at page 11, lines 28-30, and at page 25, line 21 to page 26, line 25. With respect to claims 96 and 99, support for "wherein said fragment is no greater than about 8 amino acids in length" can be found throughout the specification, e.g., at page 26, lines 26-31. With respect to claim 100, support for "wherein the IL-8 fragment comprises SEQ ID NO: 8" can be found throughout the specification, e.g., at page 27, lines 12-18. With

respect to claim 101, support for "wherein the IL-8 fragment comprises SEQ ID NO: 9" can be found throughout the specification, e.g., at page at page 27, lines 12-21.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on October 31, 2002. Applicants submit herewith a Supplemental Information Disclosure Statement (Form 1449).

Objections to the Claims

Claims 8, 89 and 91 were objected to for depending from a rejected claim. Applicants have amended these claims to be independent claims, which include the elements of the rejected claim. With respect to claim 8, elements that are inherent in the sequences recited in this claim have been omitted in the interest of greater clarity. Because these pending claims no longer depend on a rejected claim, the objection with respect to these claims should be withdrawn.

35 U.S.C. §112, Second Paragraph.

Claims 6 and 7 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Action alleges that "[t]he claims are indefinite in the recitation of 70% or 90% identical to the N-terminal amino acid sequences because it is unclear what amino acid residues are encompassed in the N-terminal amino acid sequence." Action at page 4 and previous Action at page 7.

Applicants have amended claims 6 and 7 to be independent claims. Pending claims 6 and 7 include the elements of their previous independent claim 1, e.g., an ELR motif, no greater than about 15 amino acids in length, etc., and the element "wherein the N-terminal amino acid sequence comprises a subsequence of residues of 1-36 of SEQ ID NO.: 5 or residues 1-38 of SEQ ID NO.: 4." Applicants submit that one of skill in the art would readily understand what amino acids residues are encompassed in the N-terminal amino acid sequence. As the metes and bounds of the pending claims 6 and 7 would be clear to one of skill in the art, Applicants submit that the claims are clear and definite. Withdrawal of the § 112, second paragraph, rejection is respectfully requested.

35 U.S.C. §112, First Paragraph.

Claims 3, 87 and 93 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not be enabled by the specification. Action at page 3-4. Applicants have canceled claim 3. Thus, the rejection with respect to this claim is moot. As the rejection is applied to claim 87 and 93, Applicants traverse.

The Examiner alleges that the specification is not enabling for cyclic polypeptides. The Examiner cites a paper (Ngo et al.) as supporting this allegation. Applicants submit that this paper does not support an enablement rejection of the pending claims. This paper is directed to the problems associated with predicting protein-structure using, e.g., protein-structure prediction algorithms. The paper does not directly discuss cyclic polypeptides. Thus, the paper is not relevant to the enablement issue.

Section 112, first paragraph, requires that the specification be commensurate with the claims. Accordingly, to satisfy § 112's enablement requirement, the specification must teach one skilled in the art how to produce and screen cyclic polypeptides that have the activity to stimulate the differentiation of fibroblasts to myofibroblasts. The specification is enabling for cyclic polypeptides. These cyclic polypeptides are easily made as indicated in the specification, e.g., at page 29, lines 21 to page 33, line 11, and screened using the guidance provided in the specification, e.g., by immunoblotting (e.g., at page 69, lines 28 to page 70, line 9, and at page 74, lines 4-11), by collagen gel contraction (e.g., at page 70, lines 10-19, and at page 74, lines 12-20), etc.

Based on the detailed teachings of the specification, including the guidance in the specification, the specifically defined nature of the invention, the state of the art and the level of skill in the art at the time the application was filed, Applicants submit that one of ordinary skill in the art to which this application pertains would have been reasonably able to carry out Applicants' claimed composition at the time of filing. No undue experimentation would have been required. Even if some experimentation were necessary to carry out the claimed compositions, such experimentation would clearly not support an enablement rejection of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir., 1984). It has long been established that enablement is not precluded even if some experimentation is required, provided that the amount of experimentation is not "unduly extensive." *Atlas Powder Co.*, 750 F.2d at 1576.

The Examiner appears to base the enablement rejection solely on allegedly inherent difficulties in anticipating the effects of the biological activity of a cyclic IL-8 peptide versus its linear counterpart. Office Action at page 3-4. As explained above, Applicants believe that this rationale does not support an enablement rejection of the pending claims.

The Examiner asserts that "[t]he specification fails to consider the dynamics of protein folding and the effect on receptor binding. The literature suggests that regions directly involved in binding and in providing the correct three-dimensional spatial orientation of binding and active sites are critical to the protein's structure/function relationship (Ngo et al.)." Action at page 4. However, the specification expressly describes how to produce and screen cyclic polypeptides for those that have the activity to stimulate the differentiation of fibroblasts to myofibroblasts. Thus, the specification is enabling for cyclic polypeptides and the rejection with respect to claims 87 and 93 should be withdrawn. Accordingly, withdrawal of the rejection is respectfully requested.

35 U.S.C. §102.

Claims 1, 4, 88, and 90 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Stern et al., U.S. Patent No. 5,641,867. Applicants have canceled claim 1 and 4, thus rendering the rejection with respect to these claims moot. As the rejection is applied to currently amended claim 88 and 90, Applicants traverse.

With respect to claim 88 and 90, in order for a reference to anticipate an invention, anticipation requires that "all [elements] of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983). Applicants have amended claim 88 and 90 to include the phrase language "consists of." Specifically, claim 88 states that the IL-8 fragment "consists of the amino acid sequence SAKELR (SEQ ID NO.:8)" and claim 90 states that the IL-8 fragment "consists of the amino acid sequence AVLPRSAKELR (SEQ ID NO.: 9)." The specific IL-8 fragment of claim 88 and/or 90 is not found Stern et al. Because all the elements of claim 88 and/or 90 are not found in Stern et al., the rejection of pending claims 88 and 90 with respect to 35 U.S.C. § 102(b) should be withdrawn. Thus, Applicants request withdrawal of the rejection.

35 U.S.C. §103(a).

Claims 19 and 92 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Stern et al., U.S. Patent No. 5,641,867 in view of Gosselin et al., U.S. Patent No. 5,900,235.

Applicants have canceled claim 19, thus the rejection with respect to this claim is moot. As the rejection still applies to claim 92, Applicants traverse.

Specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In the claims pending upon entry of this amendment, claim 92 depends on claim 88, 89, 90 or 91. With respect to claim 92's dependence on Claims 89 and/or 91, Stern et al., U.S. Patent No. 5,641,867, and/or Gosselin et al., U.S. Patent No. 5,900,235, do not provide all the elements of claim 89 and/or 91.

Claim 89 recites "[a] polypeptide comprising a single interleukin-8 (IL-8) fragment…the IL-8 fragment comprises an amino acid sequence variant…wherein the amino acid sequence variant that has a conservative amino acid substitution of one amino acid of the SAKELR (SEQ ID NO.:8)." Claim 91 recites "[a] polypeptide comprising a single interleukin-8 (IL-8) fragment…the IL-8 fragment comprises an amino acid sequence variant…wherein the amino acid sequence variant that has a conservative amino acid substitution of one amino acid of the AVLPRSAKELR (SEQ ID NO.: 9)." Because claim 92 depends on claim 89 and/or 91, the elements of these claims are incorporated into claim 92. These elements are not found in Stern et al.

Stern et al. teach a 12-amino acid long IL-8 peptide derived from the ELR-region of IL-8, which was used as a control in studies involving a peptide derived from the C-terminal portion of endothelial monocyte activating polypeptide (EMAP II). *See*, Stern et al. column 21, line 15-57. No other variants of IL-8 peptides are disclosed in Stern et al. Thus, all of the elements of claim 92 with 89 and/or 91 are not found in Stern et al. Furthermore, Gosselin does not provide the missing elements. Gosselin refers to therapeutic uses of IL-8, and analogues of IL-8; but, Gosselin does not disclose the specific fragments of IL-8 or the variants as recited in claims 89 and/or 91. Thus, the references, either alone or in combination, fail to provide all the elements of claim 92 (either claim 92 with 89 or claim 92 with 91). Therefore, a *prima facie* case of obviousness has not been

established because at least the first requirement of a *prima facie* case is not met with respect to claim 92, to the extent that it depends on claims 89 and/or 91.

With respect to claim 92's dependence on 88 or 90, a *prima facie* case of obviousness is also not established. Applicants have amended claim 88 and 90 herein to include the phrase "consists of" as described above under the 35 U.S.C. § 102(b) section. Claim 92 depends on claim 88 and/or 90; thus, all the elements of these claims are incorporated into claim 92. For the reasons discussed above, all the elements of claim 88 and/or 90 are not found in Stern et al. Thus, all of the elements of 92 are also not found in Stern et al. In addition, Gosselin does not remedy this deficiency. Gosselin does not describe the specific sequences of IL-8 as recited in claims 88 and/or 90. As a result, a *prima facie* case of obviousness has not been established for claim 92 to the extent that it depends on claims 88 or 90 because all the elements of the claims are not found in the references, either alone or in combination. As the first requirement for establishing a *prima facie* case has not been met for claim 92, Applicants request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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